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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hans-Michael EGGENWEILER et al.

Examiner: San Ming R. Hui

Serial No.: 10/750,878

Group Art Unit: 1617

Filed: January 5, 2004

Title: IMIDAZOLE DERIVATIVES AS PHOSPHODIESTRASE VII INHIBITORS

**BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37**

Mail Stop Appeal Brief - Patents  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

This is an appeal from the decision of the Examiner finally rejecting claims 1-6, 10, 11, 14 and 15 of the above-identified application.

**(1) REAL PARTY IN INTEREST**

The present application is assigned of record to Merck Patent GmbH, by means of an assignment recorded at Reel 013027, Frame 0668.

**(2) RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences.



#### STATUS OF THE CLAIMS

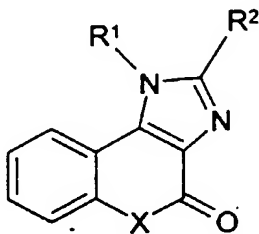
Claims rejected: 5-8  
Claims pending: 5-8  
Claims allowed: (none)  
Claims canceled: 1-4  
Claims withdrawn: 9, a petition of the restriction requirement having been filed concurrently with this appeal.  
Claims on Appeal: 5-8.

#### (4) STATUS OF AMENDMENTS

There were no amendments filed subsequent to a final rejection.

#### (5) SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to a method of treating allergic disorders, asthma, chronic bronchitis, atopic dermatitis, psoriasis, skin disorders, inflammatory disorders, autoimmune diseases, osteoporosis, transplant rejection reactions, cachexia, tumor growth, tumor metastases, sepsis, or atherosclerosis comprising administering, to a host in need thereof, an effective amount of a compound of formula I



in which

R<sup>1</sup> is H, A, benzyl, indan-5-yl, 1,2,3,4-tetrahydronaphthalen-5-yl, dibenzothien-2-yl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, A-CO-NH, benzyloxy, alkoxy, COOH or COOA,

R<sup>2</sup> is H or A,

X is O or S,  
Hal is F, Cl, Br or I,  
A is alkyl with 1 to 6 C atoms,  
or a physiologically acceptable salt or solvate thereof.

See the specification at page 1, line 4-30.

#### **(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

The only issues for consideration on appeal are the rejections under 35 U.S.C. §112, first paragraph.

#### **(7) APPELLANTS' ARGUMENTS**

Claims 5-8 have been rejected in three separate rejections under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The first rejection, spanning pages 2-6 of the office action, concerns the recitation in the claims of the treatment of "tumor growth." The second rejection, spanning pages 7-10 of the final rejection, concerns the recitation in the claim of the treatment of "autoimmune diseases." The third rejection, spanning pages 10-12 of the final rejection, concerns the alleged recitation in the claims of "memory disturbances."

(At the outset, it is noted that memory disturbances are not recited in the claims. Thus, this portion of the rejection is moot.)

With respect to the remaining two rejections, based on the recitation of treatment of tumor growth and other autoimmune diseases, the discussion in the relevant pages of the final rejection is essentially duplicative, each rejection going through a boiler plate recitation of the decision in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). Because these portions of the final rejection are largely duplicative, applicants will not burden the record for consideration by the board with discussing each rejection separately, but will discuss both rejections together. However, it is submitted that, inasmuch as the office action has made two separate rejections, over two different utilities recited in the claim, the rejection of each utility must be considered separately, on the merits.

The thrust of the relevant rejections in the final rejection is the argument that the specification "does not provide sufficient information that all tumors are treatable by the herein claimed compounds" (see page 2 of the Final Rejection), and that the specification, while enabling for rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus and ulcerative colitis does not provide enablement for *other* autoimmune disorders (see page 7 of the Final Rejection). Appellants respectfully disagree with this analysis.

First, at page 2, lines 11 - 31 of the appellants' specification, it is taught that the compounds of formula I inhibit PDE VII, and this statement is supported with a discussion of the methods used to determine this activity in the subject compounds. At page 3, lines 8 - 22 of the specification, it is taught that the compounds show an antagonistic effect on the production of TNF alpha, and thus are useful to treat all immune diseases, including, *for example*, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes, ulcerative colitis, transplant rejection reactions, cachexia and sepsis. At page 3, lines 30 - 33, it is taught that PDE VII inhibitors may also inhibit the growth of tumor cells and "are therefore suitable" for tumor therapy analogously to PDE IV inhibitors. Clearly, this discussion, *without more*, is sufficient to establish utility of the application for purposes of §112 of the statute as it constitutes a scientifically supportable statement of utility which would be plausible to one of ordinary skill in the art.

It is well established that an unsupported suggestion that reactants within a class defined by claims in a typical method of use application would not work, or that such claims embrace inoperative members, is insufficient basis alone for rejecting the claims. See *Ex parte Janin*, 209 U.S.P.Q. 761 (POBA 1979). In fact, it is clear that recitations in an Appellants' specification *must* be taken by the PTO as an assertion that all compounds encompassed in the claims are operative in the invention, in the absence of reasons or evidence to the contrary. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971).

The first paragraph of 35 U.S.C §112 requires only *objective* enablement. Where a specification teaches the manner and process of making and using the invention, the specification *must* be taken as sufficient under §112, unless there is reason to doubt the truth of these statements. See *Marzocchi, supra*. Appellants' specification clearly enables one to make and use the disclosed

compounds in the claimed methods, as evidenced from the disclosure at page 5 - 7 setting forth pharmaceutical formulations and dosages, and from the examples which also detail the production of a pharmaceutical formulations.

It is accordingly submitted that the Examiner has not provided any such reasons or evidence to doubt the assertion of utility in the specification and, thus, the further steps of the analysis as set forth in *Marzocchi* are not reached. The "complex nature of the subject matter" which is "greatly exacerbated by the breadth of the claims" does not rise to the level of such reasons or evidence. As clearly stated in *Marzocchi*, mere *breadth* of the claims does not, without more, result in non-enablement. As the court stated,

Turning specifically to the objections noted by the Board as indicated above, it appears that these comments indicate nothing more than a concern over the *breadth* of the disputed term. If we are correct, then the relevance of this concern escapes us. It has never been contended that Applicants, when they included the disputed terms in their specification, intended only to indicate a single compound. Accepting, therefore, that the term is a generic one, its recitation must be taken as an assertion by Applicants that all of the 'considerable number of compounds' which are included in the generic term would, as a class, be operative to produce the asserted enhancement of adhesion characteristics. The only relevant concern of the patent office under these circumstances should be over the *truth* of any such assertion. The first paragraph of §112 requires nothing more than *objective enablement*. How such a teaching is set forth, either by the use of illustrative examples or by broad term analogy, it is of no importance.

*Marzocchi, supra.* (Emphasis in original.) Thus, the concern expressed at pages 3 and 7 of the Office Action, apparently that the terms used in the claimed methods are broad, does not provide the reasons or evidence necessary in *Marzocchi* to pass beyond the necessity merely for objective enablement.

Further, in this regard, it is important to note, as a matter of law, that it is not necessary for Appellants' *method* claims to exclude inoperative embodiments, inasmuch as the claims are interpreted in light of the level of understanding one of ordinary skill in the art and, for methods, are

interpreted to be *per se* functional. See *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976) and *In re Dinh-Nguyen*, 492 F. 2d 856, 181 U.S.P.Q. 46 (CCPA 1974). These cases state that, for method claims, inoperative embodiments are not encompassed therein and the only question is whether it would be undue experimentation for one of ordinary skill in the art to determine the scope of the claim. This issue is discussed more fully below. Moreover, anti-tumor utilities are no longer to be considered to be "special", i.e., *per se* incredulous, by the Patent and Trademark Office. See *Ex parte Rubin*, 5 U.S.P.Q. 2d 1461 (BPAI 1987). As such, applications claiming these methods are, therefore, no more than typical method of use applications wherein the existence of reliable screening protocols correlatable with pharmaceutical activity in humans is sufficient to satisfy §112, in the absence of reasons to the contrary. As noted above, screening protocols for determining the efficacy of the compounds in the anti-tumor utilities are set forth in the specification where it is indicated that the details of using a given compound can be determined by routine testing using a known protocol which is correlated with human activity, again, see page 2, lines 18 - 31 and page 3, lines 30 - 34.

Thus, the only way that the issue of "undue experimentation" come up is if the PTO were to furnish reasons or evidence why the objective enablement of the present specification fails (none have been advanced) or it is alleged it would have been undue experimentation to determine the *scope* of the present method claims. This allegation has not been advanced, other than for the skin disorders" utility which is no longer at issue herein. Thus, the discussion of *In re Wands*, taking up a substantial amount of the Office Action, does *not* provide the necessary reasons or evidence as to why utility is deficient, but instead is reached only in other circumstances. However, since this analysis has been given considerable space in the Office Action, it will be addressed herein.

With respect to the nature of the invention, the *complexity* is in fact not supported by the breadth of the claim, as argued, for example, at page 3. In actuality, the nature of the invention is *not* complex, inasmuch as the use of PDE inhibitors to treat various indications is well established and would be well understood by one of skill in the art. With respect to autoimmune disorders noted at page 8 of the Office Action, in fact the Office Action recognizes that various types of autoimmune disorders *are* enabled by the present specification. There are no reasons why those indications singled out as non-enabled are selected.

With respect to the breadth of the claims, it is important to note that a determination of undue experimentation must be considered on a *compound by compound* basis. The mere fact that a claim is broad does *not* mean that it is undue experimentation is required to determine enablement of the compounds therein, if it is not undue experimentation to determine enablement for *each* compound in the scope of the claim. See, for example, *In re Colianni*, 561 F.2d 220, 195 U.S.P.Q. 150 (CCPA 1977). One of ordinary skill in the art can easily determine, with the protocols given in the specification, whether a given compound has the utility stated. Thus, the mere fact that many compounds must be tested is not dispositive of a lack of utility.

With respect to the guidance given by the instant specification, is submitted that the guidance is adequate. Inasmuch as pharmaceutical formulation information is given, one of ordinary skill in the art can clearly prepare the compounds for administration, dosages are given and the pharmaceutical art is well developed and administration of a compound for a given indication is quite routine. The discussion at pages 4 and 8 of the Office Action appears to be speculation on the part of the PTO that mechanisms are not well understood, however, elucidation of a mechanism is *not* necessary, where sufficient instruction is given to administer the compounds to produce the desired effect. Thus, it is submitted that this is also a non-issue.

With respect to working examples, it is well established that working examples are *not* required to provide enablement. See, for example, *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642 (CCPA 1970).

With respect to the state of the art, PDE inhibitors are well known to be implicated in signaling pathways which are instrumental in the formation of tumors. Thus, it is again not seen that this is an issue. With respect to the quantity of invention necessary, this has been discussed above. It is maintained that the fact that a claim may be broad does not, in and of itself, result in undue experimentation, if the testing of, for example, each type of cancer or each autoimmune disorder is routine. Thus, this is not seen to be basis for lack of enablement.

The only rebuttal to Appellants' discussion in the prior reply is that found at page 13 of the Final Rejection, where it is alleged that Carter provides evidence rebutting Appellants' objective enablement. Appellants strenuously disagree. The cited pages of the Carter text book disclose various drug-tumor "interactions". They appear to suggest that some drugs do not "interact" with

tumors located in the various areas listed, while others do. There is no explanation of this "interaction" and whether its significance translates to therapeutic modalities. There is no indication of the methodology used to determine the "interaction", and it is far from evident from Carter that even the "lack of interaction" translates to a *lack of therapeutic utility*. The drugs listed in the text all differ from those employed in the present claims.

It is argued in the advisory action that Carter teaches that there is no one class of compounds that would work for all tumors. Carter falls far short of such a teaching, and moreover is deficient in allowing broad conclusions to be drawn, much less conclusions respecting the presently claimed methods and compounds, in view of the deficiencies discussed above. Moreover, even if it is true, as alleged in the office action, that Carter provides evidence to doubt Appellants' statement of objective enablement in the specification, such does not, *per se* establish undue experimentation as apparently alleged in the Advisory Action. Instead, as discussed at length above, the question is then whether one of ordinary skill in art could routinely make and test each compound, for a given utility, in order ascertain whether a given compound is operative in the claimed method. It is again stressed that, in view of the screening tests given in the specification such a determination involves no more than routine skill and, thus, does not constitute undue experimentation.

Again, it is stressed that the legal standard does not take into account the breadth of the claim, nor the number compounds and methods which must be tested, so long as each individual test is routine. Since that is the present situation, it is clear that the rejection under 35 U.S.C. § 112 must be overturned and the same is respectfully requested. It is accordingly submitted that the claims are in condition for allowance.

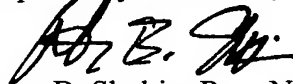
#### **(8) CONCLUSION**

For all of the above reasons, it is urged that the decision of the Examiner rejecting claims 5-8, on appeal, is in error and should be reversed.



The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



Harry B. Shubin, Reg. No. 32,004  
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO  
& BRANIGAN, P.C.  
Arlington Courthouse Plaza 1, Suite 1400  
2200 Clarendon Boulevard  
Arlington, Virginia 22201  
Telephone: (703) 243-6333  
Facsimile: (703) 243-6410

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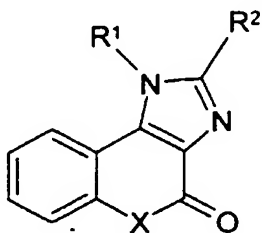
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APPENDIX OF CLAIMS ON APPEAL

5. A method of treating allergic disorders, asthma, chronic bronchitis, atopic dermatitis, psoriasis, inflammatory disorders, autoimmune diseases, osteoporosis, transplant rejection reactions, cachexia, tumor growth, tumor metastases, sepsis, or atherosclerosis comprising administering, to a host in need thereof, an effective amount of a compound of formula I



in which

R<sup>1</sup> is H, A, benzyl, indan-5-yl, 1,2,3,4-tetrahydronaphthalen-5-yl, dibenzothien-2-yl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, A-CO-NH, benzyloxy, alkoxy, COOH or COOA,

R<sup>2</sup> is H or A,

X is O or S,

Hal is F, Cl, Br or I,

A is alkyl with 1 to 6 C atoms,

or a physiologically acceptable salt or solvate thereof.

6. A method according to claim 5, wherein the autoimmune disorder is rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus, ulcerative colitis or AIDS.

7. A method according to claim 5, wherein the compound of formula I is

1-Phenyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Benzyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Cyclohexyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Cyclopentyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Butyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Isopropyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Propyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Ethyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Methyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
[1]Benzopyrano[3,4-d]imidazol-4-(1H)-one,  
2-Methyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,

1-Phenyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Benzyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Cyclohexyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Cyclopentyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Butyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Isopropyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Propyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Ethyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Methyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
[1]Benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
2-Methyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(2-Chlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(4-Methyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(4-Fluorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(2,4-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(3-Chlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,

1-(2,4-Dichlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(2,5-Dichlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(4-Acetamido-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(2-Fluorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(3-Fluorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(2-Benzoyloxy-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(2,6-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(Indan-5-yl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(2-Methoxy-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(2,3-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-(1H)-4-one,  
 1-(2,3-Dichlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(3-Chloro-4-methyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(2,5-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(4-Chlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(1,2,3,4-Tetrahydronaphthalen-5-yl)-[1]benzopyrano-[3,4-d]imidazol-4-(1H)-one,  
 1-(Dibenzothien-2-yl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-(3-Methoxy-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, or  
 1-(4-Carboxy-2-methyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one.

8. A method according to claim 6, wherein the compound of formula I is

1-Phenyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-Benzyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-Cyclohexyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-Cyclopentyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-Butyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-Isopropyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-Propyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
 1-Ethyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,

1-Methyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
[1]Benzopyrano[3,4-d]imidazol-4-(1H)-one,  
2-Methyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,

1-Phenyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Benzyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Cyclohexyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Cyclopentyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Butyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Isopropyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Propyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Ethyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-Methyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
[1]Benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
2-Methyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(2-Chlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
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1-(4-Fluorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(2,4-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(3-Chlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
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1-(2,5-Dichlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(4-Acetamido-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(2-Fluorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
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1-(2-Benzyloxy-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(2,6-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(Indan-5-yl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(2-Methoxy-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,

1-(2,3-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-(1H)-4-one,  
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1-(2,5-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(4-Chlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(1,2,3,4-Tetrahydronaphthalen-5-yl)-[1]benzopyrano-[3,4-d]imidazol-4-(1H)-  
one,  
1-(Dibenzothien-2-yl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,  
1-(3-Methoxy-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, or  
1-(4-Carboxy-2-methyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one.

## **EVIDENCE APPENDIX**

[none]

## **RELATED PROCEEDINGS APPENDIX**

[none]